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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/997,614	11/15/2001	David Botstein	P2730P1C29	7398

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EXAMINER	
WEGERT, SANDRA L	
ART UNIT	PAPER NUMBER
1647	
MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/997,614	BOTSTEIN ET AL.	
	Examiner	Art Unit	
	SANDRA WEGERT	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 January 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *119-126 and 129-131* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *119-126 and 129-131* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *15 November 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/23/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

Status of Application, Amendments, And/Or Claims

The amendment and the Remarks/Arguments submitted 23 January 2009 have been received and considered. Claims 1-118, 127 and 128 are canceled. Claims 119, 120, 121, 122 and 123 are amended. Claims 119-126 and 129-131 are under examination.

Maintained Objections and/or Rejections

35 U.S.C. §§ 101 and 112, First Paragraph - Utility, Enablement

35 U.S.C. 101 reads as follows:

> **Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.**

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> **The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.**

Claims 119-126 and 129-131 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a credible, specific, and substantial asserted utility or a well established utility.

Claims 119-126 and 129-131 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a credible, specific, and

substantial asserted utility or a well established utility, one skilled in the art clearly would not know how to use the claimed invention.

In the interest of clarity, the basis of the maintained rejections is set forth here:

The claims are directed to an isolated polypeptide having at least 80% amino acid sequence identity to SEQ ID NO: 349. Dependent claims are directed to polypeptides having 85-99% sequence identity to SEQ ID NO: 349, as well as polypeptides fused to heterologous polypeptides and polypeptides encoded by the cDNA deposited under ATCC accession number 203044.

Applicants have gone on the record as relying upon the gene amplification assay as providing utility and enablement for the claimed polypeptides. See Remarks/Arguments (received 23 January 2009) at p. 7.

At pages 539-555 of the specification, Example 170 discloses a gene amplification assay in which genomic DNA encoding PRO1097 had a ΔCt value of at least 1.0 for 2 out of 14 lung tumors and 3 out of 10 colon tumor samples when compared to a pooled control of blood DNA from several healthy volunteers. Example 170 asserts that gene amplification is associated with overexpression of the gene product (i.e., the polypeptide), indicating that the polypeptides are useful targets for therapeutic intervention in cancer and diagnostic determination of the presence of cancer (p. 539, lines 21-24). At page 548, ΔCt is defined as the threshold PCR cycle, or the cycle at which the reporter signal accumulates above the background level of fluorescence. The specification further indicates that ΔCt is used as "a quantitative measurement of the relative number of starting copies of a particular target sequence in a nucleic acid sample when

comparing cancer DNA results to normal human DNA results." It is noted that at page 548 it is stated that samples are used if their values are within 1 Ct of the normal standard human DNA. It is further noted that the ΔCt values at pages 550-554 are expressed with values to one one-hundredth of a unit (e.g. 1.29).

As discussed in the previous Office Action (25 September 2008, pp. 3-17) there are several problems with the data provided in Example 170 of the instant Specification. For example, the art recognizes that lung and colon epithelium can be aneuploid even when it is not cancerous (see Hittelman, et al, 2001, Ann. N. Y. Acad. Sci. 952:1-12, esp. p. 4, of record; Fleischhacker et al., 1995, Modern Pathology 8:360-365, of record; see especially p. 360, 1st paragraph of introduction). The gene amplification assay in the instant specification does not provide a comparison between the tumor samples and corresponding normal epithelial tissues, and does not correct for aneuploidy. Thus it is not clear that PRO1097 is amplified in cancerous colon epithelium or lung tissue more than in damaged (non-cancerous) colon epithelium or lung tissue. One skilled in the art would not conclude that PRO1097 is a diagnostic probe for cancer unless it is clear that PRO1097 is amplified to a clearly greater extent in true tumor tissue relative to non-cancerous tissue of the same origin. These problems with the data are also magnified by the fact that only a *minority* of tumor samples demonstrated gene amplification, according to Example 170 of the Specification (see Table 9B).

In addition, even if the data had been corrected for aneuploidy and a proper control had been used, the data have no bearing on the utility of the PRO1097 polypeptides. In order for the PRO1097 polypeptide to be overexpressed in tumors, amplified genomic DNA would have to correlate with increased polypeptide levels. As discussed in the last Office Action (25

September 2008, pp. 14) and contrary to Applicants' arguments (Remarks, 23 January 2009, p. 7, for example) no data regarding PRO1097 polypeptide levels in lung or colon tumors have been brought forth on the record. And, as discussed in the previous Office Action (25 September 2008, pp. 14 and 15), a positive correlation between genomic DNA levels and polypeptide levels cannot be presumed (Pennica et al., 1998, PNAS USA 95:14717-14722, of record).

Applicants maintain that "in general, there is a correlation between mRNA levels and polypeptide levels" (Remarks, pp. 7 and 8), and cite the Goddard Declaration (submitted under 37 § CFR 1.132, submitted 28 October 2005) and Pennica et al (of record) as support. However, as discussed in previous Office actions (25 September 2008 and 21 March 2007) the Goddard Declaration discusses the accuracy of the Taq DNA polymerase assay, and cites several references that attest to the use of the assay in diagnosing and prognosticating disease. Such a discussion evinces that the instant application provides a mere invitation to experiment, and not a readily available utility. In fact the accuracy of the gene amplification assay is not in doubt, only that gene amplification does not suggest a function for the claimed polypeptides, nor for the PRO1097 gene. Furthermore, the fact that it may be "more likely than not" that gene amplification is associated with expression of the gene product-which the examiner does not agree with- does not predict what the *specific* result would be for the gene product of PRO1097.

Applicants also discuss the references submitted in the instant application, such as Orntoft et al, Hyman, et al and Pollack et al, that demonstrate that "in general, gene amplification increases mRNA expression" (Remarks, p. 10). Applicants' arguments have been fully considered but they are not persuasive for the following reasons: As discussed in the previous Office actions (21 March 2007 and 25 September 2008), the Specification only discloses

measuring PRO1097 DNA in samples of colon or lung tumors. There is no measurement of corresponding mRNA levels. Therefore, the arguments pertaining to the usefulness of mRNA levels simply have no bearing on the utility of the claimed PRO1097 polypeptides. Furthermore, all three references were published in 2002, well after the priority date. Utility is determined as of the filing date. *In re Brana*, 51 F.3d at 1567. It is noted that Godbout et al., Hanna and Mornin, and Pennica et al., all of which support the rejection, were each published close to the priority date of the instant application.

Applicants also discuss the usefulness of the gene amplification assay to enable "more accurate tumor classification" (Remarks, p. 8) or to diagnose "pre-cancerous lesions" or to assay tissues for "cancer risk" (Remarks, p. 9) and cite the Ashkenazi Declaration (filed 28 October 2005). Applicants' arguments have been fully considered but are not persuasive for the following reasons: Such uses for PRO1097 are not specific, but can be said to be true for many other gene products besides PRO1097. In other words, expression levels of any gene product in cancerous tissue would be informative, but does not represent a *specific* use for PRO1097. In addition, the Ashkenazi Declaration itself appears to express uncertainty about a specific and substantial utility for PRO1097, stating "if gene amplification results in over-expression" and "even in the absence of over-expression of the gene product, amplification of a cancer marker gene [ ] is useful in the diagnosis or classification of cancer," thus acknowledging that there may not be increased expression of gene product associated with PRO1097 after all (28 October 2005, paragraphs 5-6). The Ashkenazi declaration also acknowledges that "An increase in gene copy number can result not only from intrachromosomal changes but also from chromosomal aneuploidy" (paragraph 5) thereby confirming arguments made above by the examiner

concerning aneuploidy in colon and lung epithelial tissue. It is also important to note that the specification never asserts a utility for PRO1097 involving tumor classification or diagnosis of pre-cancerous lesions or cancer risk. Thus, the Ashkenazi declaration and Applicants' arguments contradict the assertion of utility in the specification, which is that PRO1097 is diagnostic for cancer alone.

Applicants also discuss the validity of the pooled blood controls used in the present application (Remarks, p. 11, referring to the Office action of 25 September 2008, p. 10). Applicants argue that Bieche et al. (of record) used normal leukocyte DNA derived from a small subset of breast cancer patients and note that the results of the study are consistent with those reported in the literature. Applicants conclude from this study and that in Pennica, et al and Pitti, et al (of record) that the art demonstrates that pooled normal blood samples are considered to be valid negative controls for gene amplification experiments.

Applicants' arguments have been fully considered but are not found to be persuasive. Specifically, although Pennica et al. and Pitti et al. compare gene amplification of specific genes in colon and lung tumors to pooled DNA from 10 healthy normal donors, Pennica et al. and Pitti et al. are not attempting to utilize the data generated from the experiments for diagnostic purposes (as is Example 170 of the instant application). Secondly, Bieche et al. is simply utilizing real-time PCR to validate an assay for the detection and determination of the copy numbers of the three most frequently amplified genes in breast tumors (*myc, ccnd1*, and *erbB2*). That research group compared the results for 108 breast tumors with previous Southern-blot data for the same samples (abstract; p. 662, column 1). The genes studied by Bieche et al. were already well-known in the art to be amplified in breast cancer. Thus, in that case it was not

necessary to utilize matched normal tissue samples. Furthermore, each of Pennica et al., Pitti et al., and Bieche et al. did not rely solely upon the PCR assay using a control from blood genomic DNA to make conclusions. Pennica et al. also used controls from normal mucosa, surgical specimens, and several cell lines (p. 14718, left column). Pitti et al. also looked at northern blot analysis, ligand binding analysis, apoptosis induction analysis, and in situ hybridization analysis. Pitti et al. also ran an additional control in the PCR assays, using flanking DNA regions in tumor samples compared to blood DNA samples (p. 701, paragraph bridging the two columns). Bieche et al. relied upon Southern blotting to confirm the PCR results and note that not all samples showing PCR amplification also showed amplification by Southern blotting (p. 664, last paragraph before Discussion section). This was especially true for sequences that were amplified at low levels comparable to the levels that instant PRO1097 was shown to be amplified.

Applicants also discuss the Konopka et al, Godbout et al, Li et al, and Hanna and Mornin references (Remarks, pp. 14-16) as pertaining to the argument of whether or not mRNA levels are predictive of protein levels. As explained in the previous Office action (25 September 2008), the examiner is no longer arguing this point. As to the relationship between gene amplification and overexpression, which is relevant to a utility for PRO1097, the Ashkenazi Declaration of 28 October 2005 appears to support the concept that gene amplification is not always predictive of overexpression, thus supporting the examiner's position and contradicting the assertions in the specification that gene amplification indicates overexpression without indicating the possibility of exceptions. Furthermore, the Konopka et al., Godbout et al., Li et al., and Hanna and Mornin references support the rejection in that they show that gene amplification does not correlate with mRNA or protein overexpression.

Data pertaining to PRO1097 genomic DNA do not indicate anything significant regarding the claimed PRO1097 polypeptide. The data do not support the specification's assertion that PRO1097 polypeptides can be used as cancer diagnostic agents, or to support the Ashkenazi declaration and applicants' asserted utility that PRO1097 polypeptides can be used to classify tumors, or to diagnose pre-cancerous lesions. Significant further research would have been required of the skilled artisan to reasonably confirm that the disclosed PRO1097 polypeptides are overexpressed in any cancer to the extent that they could be used as cancer diagnostic agents; thus the asserted utility is not substantial. In addition, not all samples of tumor tissue showed amplification of the PRO1097 gene, thus making it, statistically speaking, a very poor predictor of any cancerous or pre-cancerous condition in samples of unknown tissue. In addition, in the absence of information regarding whether or not PRO1097 polypeptide levels are also different between specific cancerous and normal tissues, the proposed use of the PRO1097 polypeptides as therapeutic targets is simply a starting point for further research and investigation into potential practical uses of PRO1097 (See Brenner v. Manson, 148 U.S.P.Q. 689 (Sup. Ct., 1966)).

In view of the preponderance of evidence supporting the rejections, the utility and enablement rejections are properly maintained.

35 U.S.C. § 112, First Paragraph - Written Description

Claims 119-123 remain rejected under 35 U.S.C. 112, first paragraph, for containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed,

had possession of the claimed invention. The reasons for this rejection are given at pages 17-18 of the previous Office Action (25 September 2008).

Claims 119-123 are directed to an isolated polypeptide sequence comprising SEQ ID NO: 349. Additional claim limitations are directed to an isolated polypeptide comprising an amino acid sequence having at least 80%, 85%, 90%, 95%, and 99% sequence identity to (a) the amino acid sequence of the polypeptide of SEQ ID NO: 349, (b) the amino acid sequence of the polypeptide of SEQ ID NO: 349, lacking its associated signal peptide, or (c) the amino acid sequence of the polypeptide encoded by the full-length coding sequence of the cDNA deposited under ATCC accession number 203044; wherein the polypeptide is amplified in lung or colon tumors.

Applicants discuss the legal standards for Written Description, which the examiner does not dispute (Remarks, 23 January 2009, pp. 22 and 23). For example, Applicants cite case law relevant to determining the level of ordinary skill in the art (Environmental Designs, Ltd. v. Union Oil Co, 713 F.2d 693, 696, 218 USPQ 865, 868 (Fed. Cir. 1983), *cert. denied*, 464 U.S. 1043 (1984)). The examiner takes no issue with the discussion of what determines level of skill in the relevant art, nor of the legal tests for Written Description described by Applicants (Remarks, 23 January 2009, p. 23). However, Applicants have not described or shown possession of all polypeptides 80-99% homologous to peptides of SEQ ID NO: 349, *that are functionally equivalent to SEQ ID NO: 349*. Nor have Applicants described a representative number of species that have 80-99% homology to peptides comprising SEQ ID NO: 349, such that it is clear that they were in possession of a genus of polypeptides functionally similar to SEQ ID NO: 349.

Applicants also discuss "Example 10" of the Training manual as evidence that the instant Application complies with the Written Description requirement (see REVISED INTERIM WRITTEN DESCRIPTION GUIDELINES TRAINING MATERIALS, Accessed 17 April 2009 from: http://ptoweb.uspto.gov/patents/filecab/documents/writtendesc2.pdf).

Contrary to what has been implied by the Applicants in citing this example, the training materials do not support Applicants' arguments. Example 10 concerns process claims directed toward making hybridizing nucleic acids. Such claims have very little to do with the written description requirement of product claims directed toward polypeptides. In fact, while it is routine in the art to search for hybridizing nucleic acids under specified stringency conditions, and routine as well to make nucleic acids and polypeptides with a certain percent homology, the claims of the instant application require that the homologous polypeptides are of the same genus as SEQ ID NO: 349. This is very different from a nucleic acid whose only requirement is that it binds a given nucleic acid. In the instant case, the Written Description requirement only for SEQ ID NO: 349 has been satisfied by disclosure of SEQ ID NO: 349, but of the many other possible sequences that bear 80-99% homology, none have been made, and no others function substantially similar to SEQ ID NO: 349. Example 10 is in contrast to the instant case in which the issues primarily concern whether Applicants were in possession of the genus of polypeptides 80-99% identical to a peptide comprising SEQ ID NO: 349, and which have the same function. As discussed in the previous Office Action (25 September 2008), applicants have not made an adequate number of functionally-equivalent variants of SEQ ID NO: 349 to support the claimed genus.

Conclusion

No claims are allowed.

The prior art made of record and not relied upon considered pertinent to applicant's disclosure:

US 20030152999 (Ashkenazi et al.). It is noted that a recent Board decision in this commonly assigned case affirmed the utility and enablement rejections based on a fact pattern that is nearly identical to the one in the instant application.

THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Advisory information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sandra Wegert whose telephone number is (571) 272-0895. The examiner can normally be reached Monday - Friday from 9:00 AM to 5:00 PM (Eastern Time). If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Manjunath Rao, can be reached at (571) 272-0939.

The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (in USA or CANADA) or 571-272-1000.

SLW
14 April 2009

/Dong Jiang/
Primary Examiner, Art Unit 1646